PATENT APPLICATION
USL0013/US

MULTIVITAMIN FORMULATIONS FOR PROMOTING HEALTHY COLLAGEN, AND METHODS OF THEIR USE

This non-provisional application claims priority to U.S. provisional application serial no. 60/430,531, filed December 3, 2002, entitled MULTIVITAMIN FORMULATIONS FOR PROMOTING HEALTHY COLLAGEN, AND METHODS OF THEIR USE, which Application is incorporated herein by reference in its entirety

FIELD OF THE INVENTION

The invention relates to administering folic acid compound-containing formulations to individuals to facilitate healthy collagen production, to thereby treat or prevent conditions related to inadequate or unhealthy collagen production or to facilitate healing or production of healthy collagen-containing tissue. In exemplary embodiments the invention relates to periodically administering multivitamin formulations that contain amounts of folic acid to facilitate healthy collagen production, optionally in combination with vitamin B_{12} or vitamin B_6, and optionally in combination with other vitamins or minerals.

BACKGROUND

Multivitamin formulations are popular for supplementing dietary vitamins and minerals. Many varieties of multivitamin formulations are available, and some contain different combinations and amounts of two or more of folic acid, vitamin B_{12}, vitamin B_6, vitamins A, C, D, E, K, and minerals such as boron, calcium, magnesium, iron, etc.

Certain multivitamin formulations are described as useful for administering to individuals to treat or prevent various specific medical conditions. Examples of these conditions include osteoporosis, skin conditions, stress, cardiac health, promoting general health and dietary supplementation to pregnant women, to name only a few. Multivitamin formulations designed for such specific purposes typically include selected amounts of specific vitamins and minerals believed to be of particular value to individuals having the

stated conditions. As a single example, multivitamin tablets containing folic acid, vitamin B_{12}, and vitamin B_6 are sold to be taken daily to reduce serum homocysteine and promote cardiovascular health. Other examples of popular multivitamin formulations sometimes contain vitamins and minerals including calcium or magnesium, and may be taken for treating or preventing osteoporosis.

SUMMARY

Recently, in the context of vascular disease, a relationship has been proposed relating the amino acid homocysteine to certain collagen (see, e.g., Homocysteine and Cardiovascular Health, Heart Health Infocenter, Holisticonline.com, http://holistic-online.com/Remedies/Heart_homocysteine.htm, "Homocysteine is thought to promote atherosclerosis by directly damaging the artery and by reducing the integrity of the vessel wall, . . . as well as by interfering with the formation of collagen (the main protein in bone)). According to the invention, it is thought that the presence of excessive serum homocysteine could hinder or prevent healthy collagen production or the maintenance of healthy levels of biological collagen.

Separately, metabolization of homocysteine is thought to be important for production, formation, and maintenance of collagen in the body because sulfur from a metabolized homocysteine molecule is used in building collagen.

A variety of, i.e., at least 19, separately identifiable forms of collagen are recognized and known to be distributed in tissues including bone, tendon, skin, smooth muscle, arteries, vascular tissue, teeth, ligaments, and fetal and adolescent skeleton. (See Liu et al., "Collagen in Tendon, Ligament, and Bone Healing," *Clinical Orthopaedics and Related Research*, 318 265-278 (1995)). Collagen is also believed to have a role in healing surgical wounds. (See Harrison's Principles of Internal Medicine, 13th ed., p. 445).

According to the present invention, a variety of medical conditions referred to herein as "collagen-related conditions," are believed to relate to reduced, inadequate, or unhealthy biological amounts of collagen. These conditions may be caused by reduced amounts of healthy collagen in the body due to one or more biochemical conditions or genetic abnormalities in an individual that prevent or hinder the body's ability to produce or maintain collagen e.g., caused by an unhealthy or inadequate diet. According to the

invention, such conditions may be treated or prevented by administering multivitamin formulations containing folic acid and other optional vitamins and minerals, in amounts effective to promote or enhance collagen production, promote the proper formation of collagen, or maintain healthy levels of collagen in the body. According to the invention, the formulations containing folic acid can be administered not only to promote collagen production in individuals who have inadequate collagen levels, but also to augment normal collagen production and to maintain the health of bodily tissues having collagen, such as skin, muscles, bones, tendons, ligaments, cartilage, and other types of tissues that contain collagen. The invention therefore relates to methods of periodically orally administering folic acid and other optional vitamins and minerals in amounts effective to promote healthy collagen production and maintain healthy levels of biological collagen, thereby preventing or treating collagen-related conditions or otherwise promoting or sustaining the health of collagen-containing tissues.

In specific embodiments, the invention provides folic acid-containing formulations and methods of administering the formulations for the treatment or prevention of conditions that are or can be caused by collagen deficiencies or unhealthy or defective collagen production. The multivitamin formulations can also be used to generally promote healthy collagen production and to generally promote production of healthy tissue or maintain healthy tissue having collagen. Individuals having conditions that are either caused by a deficiency in collagen or conditions related to unhealthy or defective collagen production, or that do not necessarily have a collagen deficiency but who have a condition that can benefit from improved collagen availability (e.g., individuals who are or may be pregnant, who have a skin condition, who have a degenerative bone or skin condition, or who suffer from a tissue wound or tissue condition) are sometimes referred to herein as having a "collagen-related condition." Thus, the inventive methods do not require that a collagen deficiency or acute medical condition be present for administration of the folic acid-containing formulations described herein. The inventive methods contemplate prophylactic or preventative treatment of any collagen-related condition by administering the described formulations. The inventive methods also contemplate administering the described formulations to augment normal collagen production for the purpose of further promoting or maintaining healthy bodily tissue such as healthy skin, bone, muscles,

tendons, cartilage, ligaments, and for promoting healthy fetal bone, skin, or other developing tissue having collagen or wherein the development is affected by the presence of collagen.

Exemplary collagen-related conditions are believed to include: general collagen deficiency or inhibited, abnormal, or otherwise defective or inadequate production of collagen (e.g., caused or exaggerated by homocysteine or a body's inability to metabolize homocysteine); general and specific degenerative conditions such as degenerative bone disease, osteoporosis, Alzheimer's disease, and arthritis; tissue wounds such as muscle, skin, bone, or ligament wounds; pregnancy and conditions related to pregnancy nutrition, including general nutritional and dietary needs for proper fetal development; and skin conditions, e.g., acne, psoriasis, rash, etc.

Embodiments of the inventive methods include administering folic acid-containing formulations for: treatment or prevention of general collagen deficiency or conditions where collagen production is inhibited; treatment or prevention of degenerative bone disease such as osteoporosis; treatment or prevention of other degenerative disease such as Alzheimer's disease and arthritis; treatment of wounds or promotion of wound healing including skin wounds, muscle wounds, bone wounds, cartilage or ligament or other tissue wounds, including healing such wounds generally or for administering the formulations prior to or after surgery; promoting prenatal health and nutrition (and fetal development); and treating or preventing skin conditions and promoting healthy skin. Preferred inventive methods include the oral administration of folic acid-containing formulations.

The inventive formulations and methods may further relate to administering amounts of folic acid compound that exceed Dietary Reference Intakes ("DRIs") conventional for folic acid compounds. While folic acid compounds are known and administered for various conditions, many commercially available multivitamin formulations continue to be taken to provide daily dosages of folic acid compounds that may be below amounts required for the treatment of collagen-related conditions or for maintaining healthy collagen levels in the body. Therefore, conventional vitamin formulations may fail to provide adequate or optimal supplementation of dietary folic acid, and consequently may not sufficiently promote or facilitate healthy collagen production or otherwise be in a quantity sufficient to treat or prevent a collagen-related condition.

The inventive formulations and methods provide relatively high daily dosages of folic acid when compared to certain commercially available multivitamin formulations of similar compositions and uses, which can be administered to individuals having collagen-related conditions or to facilitate healing or production of collagen-containing tissue. The inventive formulations preferably include at least or greater than 400 micrograms (mcg), and more preferably at least 500 mcg, 1000 mcg, 1500 mcg, or 2000 mcg of a folic acid compound per dose. Such formulations having these quantities of folic acid compound can be referred to herein as "dose formulations" or "unit dose formulations" intended to be administered or taken as a single dose. In some formulations, depending on the collagen-related condition being treated, the folic acid compound can be present up to and including about 10 milligrams. The inventive methods provide for the administration of dosages greater than 400 mcg of folic acid compound per day, and in preferred embodiments, greater than 500 mcg, greater than 1 mg, 1.5 mg, and greater than 2 mg folic acid compound per day.

In some embodiments, the inventive formulations can include vitamin B_6 in a useful amount, e.g., effective for the for the treatment of a collagen-related condition or for maintaining healthy collagen levels in the body, for example from about 5 or 10 to about 50 milligrams. Vitamin B_6 is a cofactor in metabolizing homocysteine, and therefore can reduce serum homocysteine and further promote the production and presence of healthy collagen.

In some embodiments, the inventive formulations can include vitamin B_{12} in a useful amount, e.g., effective for the for the treatment of a collagen-related condition or for maintaining healthy collagen levels in the body, for example from about 15, 20, 50, 100, or 150 micrograms vitamin B_{12} up to about 1000 micrograms of vitamin B_{12}. Vitamin B_{12} is also a cofactor in metabolizing homocysteine, and therefore can also reduce serum homocysteine and further promote the production and presence of healthy collagen.

In one embodiment the invention provides formulations that specifically contain or consist of compounds that are effective for the treatment of collagen-related conditions or for maintaining healthy collagen levels in the body, optionally with other inert ingredients, for example, surfactants, cosolvents, and excipients. These may include formulations consisting of a folic acid compound, a vitamin B_6 compound, and a vitamin B_{12} compound

in amounts sufficient for the treatment of collagen-related conditions or for maintaining healthy collagen levels, and optional inert ingredients. In these formulations, the amount of the folic acid compound can be at least 400 mcg, the amount of the vitamin B_6 compound can be in the range of about 5 or 10 to about 50 milligrams, and the amount of vitamin B_{12} compound can be in the range of about 15, 20, 50, 100, or 150 micrograms vitamin B_{12} up to about 1000 micrograms. These formulations can be particularly useful, for example, when the administration of vitamins or minerals other than folic acid, vitamin B_6, and vitamin B_{12} is not necessary or is not indicated. The invention also contemplates methods of administering these formulations for the treatment of collagen-related conditions or for maintaining healthy collagen levels.

In other embodiments, the inventive formulations can include amounts of other vitamins and minerals including, but not limited to, calcium, magnesium, thiamine, riboflavin, boron, iron, vitamin A, vitamin C, vitamin D, vitamin E, vitamin K, other useful or similar substances, and combinations thereof. Multivitamin formulations as described herein do not include aspirin, and preferably do not include any other substances that would require regulatory approval of the sale or use of the folic acid compound-containing formulation.

Vitamins and minerals included in the folic acid compound-containing formulations can be selected for administering to treat or prevent specific conditions. For example, multivitamin formulations of the invention formulated and administered to treat or prevent degenerative bone disease such as osteoporosis, other degenerative tissue disease such as arthritis, Alzheimer's disease, or other degenerative conditions, in addition to containing folic acid compound, may include vitamin B_6, vitamin B_{12}, and other vitamins and minerals useful to treat or prevent such conditions, including one or more of calcium, magnesium, vitamin D, boron, or others. When compared to commercial multivitamins formulated for treatment or prevention of these or similar conditions, the inventive formulations can be formulated to provide higher dosages of one or more of these vitamins or minerals, for example a dosage of folic acid compound greater than 1 mg or 2 mg per multivitamin dosage form or per day; a dosage of boron greater than 150 or 200 mcg, e.g., greater than 500 mcg, or in the range from 1 mg to 5 mg per day, or any amount up to 20 mg boron per day; a dosage of vitamin B_6 greater than 1.7 mg per dosage

form or per day, preferably greater than 3 mg, vitamin B_6 especially from about 5 or 10 mg vitamin B_6 to about 50 or 100 mg vitamin B_6 per dosage form or per day; a dosage of vitamin B_{12} greater than 25 mcg per dosage form or per day, e.g., from about 50 mcg, 100 mcg, or 150 mcg up to about 1000 mcg vitamin B_{12} per dosage form or per day; greater than 250 mg and up to about 1000 mg calcium per dosage form or per day; and greater than 125 mg and up to about 250 mg magnesium per dosage form or per day. Therefore, in some embodiments, active ingredients of the formulation consist of a folic acid compound, a vitamin B_6 compound, a vitamin B_{12} compound, calcium, magnesium, vitamin D, and boron, in amounts described herein.

In another embodiment, formulations can be prepared to improve pre-natal health, promote fetal development, or to supplement a pre-natal diet. These formulations include folic acid, and can also include vitamin B_6, vitamin B_{12}, and other vitamins and minerals useful to improve pre-natal health or to supplement a pre-natal diet, including one or more of thiamine, riboflavin, calcium, iron, magnesium, or others. When compared to DRI values for pregnancy or commercial multivitamins formulated for pre-natal health and diet supplementation, the inventive formulations can be formulated to provide higher dosages of one or more of these vitamins or minerals. For example, the inventive methods and formulations can provide a dosage form or a daily dosage of a folic acid compound in an amount greater than 400 mcg, e.g., equal to or greater than 1 mg or 2 mg up to about 5 or 10 mg folic acid compound per day; a dosage of vitamin C in an amount greater than 90 or 120 mg, e.g., 130 or 150 mg or greater; a dosage of thiamine in an amount greater than 3 mg, e.g., 3.5 or 4 mg; a dosage of riboflavin in an amount greater than 3.4 mg, e.g., 3.5 or 4 mg or greater; a dosage of vitamin B_6 in an amount that is greater than 1.7 mg, e.g., greater than 3 mg, preferably greater than 5 mg or 10 mg, and up to about 50 mg; calcium in an amount in the range from about 200 to 1000 mg; iron in an amount greater than 18 mg, such as from 20 to 100 mg, e.g., from 30 to 60 mg.

In another embodiment, formulations for the treatment or prevention of skin conditions or to promote healthy skin, in addition to a folic acid compound, can include vitamin B_6, vitamin B_{12}, and other vitamins and minerals useful treat or prevent skin conditions or to promote healthy skin, including one or more of vitamin C, vitamin A, and vitamin E, or other vitamins or minerals. When compared to the DRI or commercial

multivitamins formulated for pre-natal health and diet supplementation, the inventive formulations can be formulated to provide higher dosages of one or more of these vitamins or minerals. For example the inventive formulations may contain a dosage of a folic acid compound in an amount greater than 1 mg; a dosage of vitamin B_{12} in an amount greater than 2.4 mcg, e.g., 100 or 200 mcg vitamin B_{12} up to about 1000 mcg vitamin B_{12}; a dosage of vitamin C in an amount greater than 90 or 120 mg, e.g., 130 or 150 mg or greater, e.g., up to 300 or 500 mg vitamin C; a dosage of vitamin E in an amount greater than 33 IU or 60 IU, e.g., 100 or 200 IU up to about 300 or 500 IU; and a dosage of niacin in an amount greater than about 16 mg, e.g., from about 18 to 30 mg niacin.

In another embodiment, formulations that promote wound healing, e.g., skin, muscle, tendon, ligament, or bone wounds, including or other than wounds cause by a surgical procedure, include folic acid compound and can also include vitamin B_6, vitamin B_{12}, and other vitamins and minerals useful for promoting wound healing, including one or more of vitamin C, vitamin E, zinc, and other vitamins or minerals. When compared to the DRI or commercial multivitamins, the inventive formulations can be formulated to provide higher dosages of one or more of these vitamins or minerals. For example the inventive formulations may contain a dosage of a folic acid compound in an amount in the range greater than 400 mcg, e.g., 1 mg or greater folic acid compound; a dosage of vitamin B_{12} in an amount greater than 2.4 mcg, e.g., 50 mcg, 100 mcg, or 200 mcg vitamin B_{12} up to about 1000 mcg vitamin B_{12}.

An aspect of the invention relates to a method of facilitating or maintaining collagen formation to treat or prevent a collagen-related condition. The method includes orally administering a formulation comprising greater than 400 micrograms of folic acid compound, preferably greater than 500 micrograms of folic acid compound, and more preferably greater than 1000 micrograms of folic acid compound.

In another aspect, the invention relates to a method of facilitating or maintaining collagen formation, the method including orally administering one or more formulation comprising greater than 400 micrograms folic acid compound, to provide a daily dosage of greater than 800 micrograms folic acid compound per day. The method can facilitate collagen formation to treat or prevent a condition such as a degenerative bone disease, osteoporosis, arthritis, or Alzheimer's disease; the method can facilitate collagen formation

to treat or facilitate healing of a skin or muscle wound; the method can facilitate collagen formation to promote post-surgical skin or muscle tissue healing; and the method can facilitate collagen formation and promote pre-natal health or fetal development.

In yet another aspect, the invention relates to a method of treating or preventing degenerative bone disease, Alzheimer's disease, or arthritis, by orally administering a formulation comprising greater than 1 milligram of a folic acid compound.

In yet another aspect the invention relates to a method of improving pre-natal health or fetal development, by orally administering a formulation comprising from about 1.5 to 10 milligrams of folic acid compound.

Another aspect of the invention relates to a method of promoting healthy skin by administering a formulation comprising greater than 400 micrograms folic acid compound. The formulation can preferably contain, vitamin B_6, vitamin B_{12}, vitamin C, vitamin E, and boron.

Yet another aspect of the invention relates to a method of promoting post-surgical health or recovery by orally administering a dietary supplement formulation comprising from about 1 to about 10 milligrams folic acid compound and from about 20 to 1000 micrograms vitamin B_{12}.

Still another aspect of the invention relates to a method of promoting healing of a skin or muscle wound by orally administering a formulation comprising from about 1 to 10 milligrams folic acid compound and from about 20 to 1000 micrograms vitamin B_{12}.

DETAILED DESCRIPTION

The invention relates to periodically administering a formulation that includes a folic acid compound to an individual in a daily dosage (e.g., daily forms or total daily amount) that promotes collagen production, promotes a healthy biological collagen level in mammals, especially humans, and promotes the formation and maintenance of healthy collagen-containing tissue in the body. In specific embodiments, the administration of folic acid-containing formulations can result in the prevention of collagen-associated disorders or can be used for the treatment of an acute collagen-related condition. Alternatively, the improved collagen production in the absence of a collage shortage or defective collagen production, or in the presence or absence of an acute medical condition,

can still promote the healthy development or healing of tissue that relies on collagen, such as healthy skin, bones, muscles, ligaments, cartilage, or fetal tissue.

Collagen is the primary protein of connective tissue, which includes cartilage, bone, tendon, teeth, and skin. Collagen (in a pre-processed form called procollagen) is assembled in cells and consists of three polypeptides wound around each other in a triple helix form and are stabilized by intrachain disulfide bonds. After the helical molecule is assembled and modified in the cell it is secreted into the extracellular medium and further processed to a mature form (tropocollagen). Tropocollagen is a large molecule having a size of about 3,000Å with a width of 14 Å. These matured collagen molecules assemble into fibrils in the extracellular space in a staggered, parallel, fashion wherein the molecules are stabilized in this fibril pattern by covalent cross-linking bonds between the N-terminus of one molecule and the C-terminus of another. The collagen fibrils further pack into hexagonal arrays to form fibril bundles. In tendons these collagen fibrils run parallel to the axis, in skin the fibrils are interlaced and branched.

Mammals have more than 30 genetically distinct collagen polypeptide chains, which make up the 19 different collagen variants that occur in different tissues. The most common are: Type I collagen, in skin, bone, tendon, blood vessels and cornea; Type II collagen, in cartilage, intervertebral disk; Type III in blood vessels, fetal skin.

In one aspect of the invention the formulations described herein can facilitate or maintain collagen formation to treat or prevent a collagen-related condition. As used herein "collagen formation" is used in its broadest sense and refers to the production of collagen, its incorporation into collagen-containing tissue (including, e.g., the synthesis, processing, crosslinking, secretion, and assembly of collagen fibrils) and the presence of healthy collagen-containing tissue. "Facilitating collagen formation," therefore, refers to the ability of a formulation described herein to positively affect the production of collagen, leading to the formation of healthy collagen-containing tissue in either physiologically normal (i.e. healthy) or disease states. Facilitating collagen formation may be brought about by the ability of the formulations described herein to promote steps, such as biochemical steps, leading to the formation of collagen fibrils. "Maintaining collagen formation," refers to the ability of a formulation described herein to preserve existing healthy collagen-containing tissue, by for example, by preventing the degradation of

collagen or by replenishing collagen to tissue wherein collagen is broken down by natural processes or disease-associated processes.

The term "folic acid compound" is used in the present description in a manner consistent with its understood meaning in the vitamin and medical arts. The term means compounds generally understood to provide vitamin (folic acid) efficacy in its administered form or as a derivative of its administered form. The term refers to compounds commonly referred to as folic acid, folinic acid, folacin, tetrahydrate folate, and pteroyl monoglutamic acid, and more generally includes all pteroglutamates having vitamin activity.

The daily oral dosage of folic acid compound administered according to the invention can preferably exceed daily recommended intakes ("DRIs") that are conventional for folic acid compounds, for certain individuals and perhaps for certain individuals having specific conditions. The DRI for folic acid compound is 400 mcg, generally, and 600 mcg for pregnant women. Table 1 lists the DRI of folic acid compound as well as selected other vitamins and minerals. According to the inventive methods and formulations, daily oral dosages can exceed one or more of these DRIs. The inventive formulations can include, for example, folic acid compound in an amount greater than 400 micrograms (mcg), 500 mcg, 600 mcg, 1000 mcg, or 1500 mcg. The amount of folic acid compound administered daily or in a dosage form can sometimes depend on the collagen-related condition being treated, and can be in an amount in the range up to and including about 5 or 10 milligrams. Total daily dosage of folic acid compound, according to the invention, can be amounts greater than a DRI and as described herein, can be taken once in a single formulation dosage form or in two or more dosages at the same or different times throughout a single day.

Table 1.

Recommended Intakes for Certain Vitamins and Minerals

NUTRIENT	CURRENT RDI*	NEW DRI**	UPPER LIMIT (UL)***
Calcium	1,000 mg (adults); National Osteoporosis Foundation recommendation 1,200 mg daily.	1,300 mg	2,500 mg
Magnesium	NIH Recommends (Daily) Men Women 18-30 years old 400 mg 310 mg 30+ years old 420 mg 320 mg	420 mg	350 mg (applies only to intake from supplements)
Vitamin D	400 IU (10 mcg) NIH Recommends (Daily) Men Women 19-50 years old 5 mcg 5 mcg 51-70 years old 10 mcg 10 mcg Over 71 years old 15 mcg 15 mcg	15 mcg (600 IU)	50 mcg (2,000 IU)
Folic acid compound	400 mcg 600 mcg for pregnant women	400 mcg food 200 mcg synthetic (400 mcg from supplements for women of child bearing age)	1,000 mcg synthetic
Vitamin B_6	2 mg	1.7 mg	100 mg
Vitamin B_{12}	6 mcg	2.4 mcg (over age 50, supplements recommended)	Not Determined
Boron	None	None	20 mg (same for all adults)

Information in this table was derived from the Council for Responsible Nutrition (2001)

* Reference Daily Intake (RDI) is the value established by the FDA for use in labeling

** Dietary Reference Intake (DRI) are the most recent set of dietary recommendations established by the Food and Nutrition Board of the Institute of Medicine

*** Upper Limit (UL) is the upper limit of intake considered safe for use by adults (unless otherwise specified, the UL combines all potential sources of nutrient)

In some embodiments, the inventive formulations can preferably include amounts of one or more other vitamins or minerals that, in combination with folic acid compound, can promote healthy collagen production, promote general nutritional and dietary health, or can be specifically selected to treat or prevent another condition that may or may not relate to collagen.

The term "vitamin B_6" is used in the present description in a manner consistent with its understood meaning in the vitamin and medical arts. The term means compounds generally understood to provide vitamin B_6 efficacy in its administered form or as a derivative of the administered form. The compounds are understood to include pyridoxine compounds such as pyridoxine hydrochloride or any other of the vitamins of the B_6 complex (i.e., codecarboxylase, pyridoxal hydrochloride, or pyridoxamine

dihydrochloride) or any precursors or analogues thereof which would give rise to vitamin B_6-like activity. Vitamin B_6 is a known cofactor in metabolizing homocysteine, and therefore can reduce serum homocysteine and further promote the production and maintenance of healthy collagen. A useful amount of vitamin B_6 in combination with the folic acid compound and any other added vitamins or minerals can promote healthy collagen by facilitating homocysteine metabolization.

The daily oral dosage of vitamin B_6 administered according to the invention can be any useful and therapeutic amount, and in certain preferred embodiments of the invention can exceed daily recommended intakes ("DRIs") that are conventional for vitamin B_6, especially for certain individuals and perhaps for certain individuals having specific conditions. The standard DRI for vitamin B_6 is 1.7 mg per day. Exemplary dosages according to the inventive methods and formulations can include at least or greater than 5 mg, 10 mg vitamin B_6 per day, and depending on the collagen-related condition being treated, up to and including 20, 50, or 100 milligrams vitamin B_6 per day. The amount of vitamin B_6 can be administered in a single dose or in more than one dose taken at the same or different times throughout the day.

The term "vitamin B_{12}" is used in the present description in a manner consistent with its understood meaning in the vitamin and medical arts. The term means compounds generally understood to provide vitamin B_{12} efficacy in its administered form or as a derivative of the administered form. The compounds are understood to include cobalamin compounds such as hydroxycobalamin, methylcobalamin, and cyanocobalamin or any other substances or any precursors or analogues thereof which would give rise to vitamin B_{12}-like activity. Vitamin B_{12} is a known cofactor in metabolizing homocysteine, and therefore can reduce serum homocysteine and further promote the production and presence of healthy collagen. A useful amount of vitamin B_{12}, in combination with the folic acid compound and any other added vitamins or minerals, can promote healthy collagen by facilitating homocysteine metabolization.

The daily oral dosage of vitamin B_{12} administered according to the invention can be any useful and therapeutic amount, and in certain preferred embodiments of the invention may exceed daily recommended intakes ("DRIs") that are conventional for vitamin B_{12}, especially for certain individuals and perhaps for certain individuals having specific

conditions. The standard DRI for vitamin B_{12} is 2.4 mcg per day. Exemplary daily dosages of vitamin B_{12}, according to the formulations and methods of the invention, can be from about 20 mcg, 100 mcg, or 150 micrograms vitamin B_{12} up to about 1000 micrograms B_{12}. The amount of vitamin B_{12} may be administered in a single dose or in more than one dose taken at the same or different times throughout the day.

The term "vitamin A" is used in a manner consistent with its understood meaning in the vitamin and medical arts. The term means compounds generally understood to provide vitamin A efficacy in its administered form or a derivative of its administered form. The compounds are understood to include β-ionone derivates possessing qualitatively the biological activity of retinol, retinol, β-carotene, and salts thereof such as the acetate or palmitate salts or any precursors or analogues thereof which would give rise to vitamin A-like activity after administration. The amounts of vitamin A to be administered per day can be any useful amount, such as an amount in the range from about 2000 to 4000 IU. The selected amount of vitamin A may be administered in a single dose or in more than one dose taken at once or at different times throughout the day.

The term "vitamin C" is used in a manner consistent with its understood meaning in the vitamin and medical arts. The term means compounds generally understood to provide vitamin C efficacy in its administered form or a derivative of its administered form. Vitamin C compounds include vitamin C in any of its forms (e.g., salts of ascorbic acid) or any precursor or analogue which would give rise to vitamin C-like activity after administration. A preferred form of vitamin C is ascorbic acid. The amounts of vitamin C to be administered per day can be any useful amount, such as an amount in the range from about 50 to 1000 mg, preferably from 100, 150, or 250 mg vitamin C to 500 mg vitamin C. The selected amount of vitamin C may be administered in a single dose or in more than one dose taken at once or at different times throughout the day.

The term "vitamin D" is used in a manner consistent with its understood meaning in the vitamin and medical arts. The term means compounds generally understood to provide vitamin D efficacy in its administered form or a derivative of its administered form. Exemplary vitamin D compounds include vitamin D_1, vitamin D_2, vitamin D_3, or vitamin D_4, or any precursor or analogue to any of these vitamins which would give rise to vitamin D-like activity after administration. The amounts of vitamin D to be administered

per day can be any useful amount, such as an amount in the range from about 200 to 600 IU (5 to 15 mcg). The selected amount of vitamin D may be administered in a single dose or in more than one dose taken at once or at different times throughout the day.

The term "vitamin K" is used in a manner consistent with its understood meaning in the vitamin and medical arts. The term means compounds generally understood to provide vitamin K efficacy in its administered form or a derivative of its administered form. Exemplary vitamin K compounds include vitamin K_1, vitamin K_2, vitamin K_3, vitamin K_4, vitamin K_5, vitamin K_6 and vitamin K_7, or any precursor or analogue to any of these vitamins (such as the naphthaquinones), which would give rise to vitamin K-like activity after administration. The amounts of vitamin K to be administered per day can be any useful amount, such as an amount in the range from about 20 to 200 mcg. The selected amount of vitamin K may be administered in a single dose or in more than one dose taken at once or at different times throughout the day.

Any other vitamin or mineral discussed herein are also is used in a manner consistent with their understood meanings in the vitamin and medical arts. The terms identify compounds generally understood to provide vitamin or mineral efficacy in an administered form or as a derivative of an administered form. Examples of these terms include calcium, magnesium, thiamine, riboflavin, boron, iron, and vitamin E. The selected amount of any one or more of these vitamins and minerals may be administered in a single dose or in more than one dose taken at once or at different times throughout the day.

Calcium is a mineral supplement that is available in a variety of different forms such as calcium carbonate (e.g., from oyster shell) (this is presently the least expensive form of calcium but is theorized to cause constipation -- still calcium carbonate can be preferred because it is very active and therefore helps to reduce dosage, e.g., tablet size for easy swallowing); calcium citrate (more available than calcium carbonate, doesn't cause constipation); calcium bi-glycinate (may be more available than calcium citrate).

CALCIUM SALT	% CALCIUM	COMMON PRODUCTS
Calcium Gluconate	9%	500 mg tablets (45 mg elemental calcium)
Calcium Lactate	13%	650 mg tablets (84.5 mg elemental calcium)
Calcium Citrate	21%	Citracal - 200 mg elemental calcium
Calcium Acetate	25%	PhosLo 667 mg (169 mg elemental calcium)
Tricalcium Phosphate	39%	Posture - 600 mg elemental calcium
Calcium Carbonate	40%	Os-Cal - 500 mg elemental calcium (1,250 mg)
		Caltrate - 600 mg elemental calcium (1,500 mg)

Calcium supplementation can be included in the formulations and methods of the invention to provide a formulation that, in addition to promoting healthy collagen, can maintain healthy bones, in particular in postmenopausal women. Increased calcium intake has been directly correlated with increased bone mass. While results from individual studies are conflicting, it does not appear that there are significant differences between the various salt forms in terms of absorption or bioavailability -- the total amount of elemental calcium is the most significant factor. Including calcium carbonate, for example at 750 mg (300 mg elemental calcium) per dosage formulation can reduce or minimize tablet size while still providing and 45% of the DRI for calcium when taken as two dosages or twice daily. Thus, exemplary daily dosages of calcium can be in the range from about 200 mg to about 1000 mg elemental calcium per day.

The inventive methods and formulation can also include administering magnesium. Magnesium can be available as any one or more of magnesium chloride, magnesium aspartate, magnesium oxide, magnesium succinate, magnesium gluconate, magnesium lactate, magnesium citrate, and as amino acid chelates. Magnesium oxide has the highest percent of elemental magnesium, and therefore can be preferred to minimize tablet size.

MAGNESIUM SALT	% MAGNESIUM	COMMON PRODUCTS
Magnesium Gluconate	5.9%	Magtrate 500 mg (29 mg elemental magnesium)
Magnesium Oxide	60.3%	Uro-Mag 140 mg (84.5 mg elemental magnesium)
		MagOx 400 mg (241 mg elemental magnesium)
Magnesium Chloride	25.5%	Slo-Mag 535 mg (64 mg elemental magnesium)
		(Slo-Mag uses chloride hexahydrate salt)
Magnesium Lactate	12%	Mag-Tab SR (84 mg elemental magnesium)
Magnesium Citrate	16.2%	Unknown

The role of magnesium supplementation in the prevention of degenerative bone disease such as osteoporosis is less well established than for calcium. Although decreased

bone mass is the hallmark of osteoporosis, qualitative changes in bone are also present. There is growing evidence that magnesium may play an important role in qualitative bone changes. In addition, adequate magnesium levels are necessary for proper calcium metabolism. Lastly, dietary intake studies consistently show that magnesium intake can sometimes or often be well below the established DRI, indicating that a number of individuals may be at risk for a magnesium deficiency. The upper limit for magnesium from supplements is established to minimize the incidence of diarrhea, which is the most common side effect of magnesium supplementation. Including 250 mg magnesium oxide (150 mg elemental magnesium) per tablet would minimize the tablet size while providing and 71% of the DRI (86% of the upper limit for supplements) for magnesium when two tablets are taken per day.

Exemplary daily dosages of riboflavin (vitamin B_2) can be in the range from about 3.5 to about 5 mg per day, but higher or lower amounts could also be useful.

Boron supplementation can be accomplished by administering boron, e.g., in the form of sodium borate, or potassium borate, boron citrate, boron aspartate, or boron glycinate (or other amino acid chelates). There is no recommended daily intake for boron, but some information suggests 2-3 mg daily for boron supplementation, and a normal daily intake through diet may be approximately, at maximum, 5 mg/day. Boron supplementation carries the following popular claims: prevents loss of magnesium, calcium, and phosphorus; prevents bone loss; and helps maintain healthy estradiol levels. Boron may have a role in vitamin D metabolism, which may indirectly impact bone development. A safe upper limit of 20 mg has been established for all adult populations (includes dietary and supplement amounts). The safe upper limit for pregnancy is 20 mg/day (based on animal reproduction studies). The maximum expected dietary consumption (including drinking water) is expected to be less than 5 mg/day. Exemplary daily dosages of boron according to the methods and compositions of the invention can be in the range from about 1 mg or 2 mg to about 5 mg per day, taken as a single dosage form or as two or more during a day.

Exemplary daily dosages of iron, according to the methods and formulations of the invention, can be in the range from about 10 to about 60 mg per day, but higher or lower dosages may also be useful.

As used herein, the term "formulation" refers to any sort of suitable dosage form used to deliver the compounds, as described herein, to a subject. Preferred formulations are oral dosage forms; however other formulations, for example, formulations for injection (e.g., subcutaneous, intramuscular, etc.), formulations for topical application, or formulations for rectal, nasal, or optical administration are contemplated and can be prepared and administered to a subject. As used herein "oral formulations" or "oral dosage forms" include any liquid composition, solid composition, or combination liquid/solid composition that can be suitable delivered to a subject. Formulations of the invention may be administered as oral dosage forms and may be. These oral dosage forms include solid dosage forms, for example, tablets, capsules, including soft elastic capsules or hard elastic capsules having a solid or liquid fill, lozenges, chewable tablets or chewable capsules, and liquid dosage forms, for example, solutions, suspensions, dispersions or syrups. Preferred dosage forms for the multivitamin composition may be capsules, soft-gel capsules, or tablets.

The formulation can include additional inactive ingredients, including, but not limited to surfactants, cosolvents, and excipients.

Surfactants, such as hydrophilic and hydrophobic surfactants, can be included in the formulations. Particular surfactants can be used based on the on the overall composition of the formulation and the intended delivery of the formulation. Useful surfactants include polyethoxylated fatty acids, PEG-fatty acid diesters, PEG-fatty acid mono- and di-ester mixtures, polyethylene glycol glycerol fatty acid esters, alcohol-oil transesterification products, polyglycerized fatty acids, propylene glycol fatty acid esters, mixtures of propylene glycol esters-glycerol esters, mono- and diglycerides, sterol and sterol derivatives, polyethylene glycol sorbitan fatty acid esters, polyethylene glycol alkyl ethers, polysaccharide esters, polyethylene glycol alkyl phenols, polyoxyethylene-polyoxypropylene block copolymers, sorbitan fatty acid esters, lower alcohol fatty acid esters, ionic surfactants, and mixtures thereof.

The formulations can also include cosolvents such as alcohols and polyols, polyethylene glycols ethers, amides, esters, other suitable cosolvents, and mixtures thereof. The formulations can also include excipients or additives such as sweeteners, flavorants,

colorants, antioxidants, preservatives, chelating agents, viscomodulators, tonicifiers, odorants, opacifiers, suspending agents, binders, and mixtures thereof.

Useful dosage forms can be prepared by methods and techniques that will be well understood by those of skill in the vitamin arts and may include the use of additional ingredients in producing tablets, capsules, or liquid dosage forms.

The formulations of the invention can be administered to promote collagen production in individuals who have or do not have a collagen-related condition, e.g., treat or prevent a collagen-related condition, or to otherwise facilitate healthy collagen production and healthy collagen tissue, for example, by maintaining healthy collagen tissue. Examples of methods according to the invention include the following:

Degenerative tissue conditions

A type of collagen-related condition is a class of degenerative bone or tissue diseases including degenerative bone disease, specifically including osteoporosis, as well as other degenerative diseases such as arthritis and Alzheimer's disease. According to the invention, the folic acid-containing formulations can be administered daily to promote collagen production and treat or prevent degenerative diseases such as osteoporosis, arthritis, and Alzheimer's disease, e.g., improve an existing degenerative condition, prevent further degeneration, or prevent degeneration before it occurs.

The dosage methods and formulations of the invention used to treat or prevent a degenerative bone or tissue disease or condition can preferably include a daily dosage of a folic acid compound in an amount that is greater than the DRI, e.g., greater than 400 mcg per day, preferably greater than 500 mcg per day, e.g., greater than 1000 or 2000 mcg per day. Such an amount can be administered, for example, in a single oral dosage or with two or more dosages taken at the same time or different times throughout the day. For example, a tablet of the invention may contain 1.1 mg of folic acid compound and two can be taken daily to provide 2.2 mg per day folic acid compound, to treat or prevent a degenerative bone or tissue disease.

In some embodiments, preferably, useful multivitamins for treating or preventing degenerative diseases such as osteoporosis, arthritis, and Alzheimer's disease, contain vitamin B_6, e.g., to provide a daily dosage of an amount in the range from about 5, 10, or

20 mg to about 50 mg per day vitamin B_6; and vitamin B_{12}, e.g., to provide a daily dosage of an amount in the range from about 100 or 150 mcg to about 1000 mcg per day vitamin B_{12}. Useful multivitamins for treating or preventing degenerative diseases such as osteoporosis, arthritis, and Alzheimer's disease, can also include one or more additional vitamins and minerals such as calcium, e.g., to provide a daily dosage the range from about 300 to about 1500 mg per day elemental calcium, e.g., from about 1000 mg to 1500 mg per day; magnesium, e.g., to provide a daily dosage in the range from about 25 to about 400 mg per day elemental magnesium; vitamin D (e.g., vitamin D_3), e.g., to provide a daily dosage in the range from about 5 to about 25 mcg vitamin D; boron, e.g., to provide a daily dosage in the range from about 1 to about 5 mg boron; as well as any other useful vitamins or minerals.

Wound healing

Another example of a type of collagen-related condition includes tissue wound such as bone, skin, muscle, tendon, ligament, cartilage, or other tissue wounds. The compositions of the invention can be administered to facilitate wound healing generally by giving daily oral dosages as described herein to an individual having a skin wound, a muscle wound, a tendon or ligament wound, or another tissue wounds whose healing can be facilitated by healthy collagen production. The method includes administering formulations as described for general wound healing such as the treatment of cuts, bruises, lacerations, contusions, muscle or cartilage tears, skin sores, or other similar or related tissue wounds. In preferred embodiments the formulations are administered orally or topically. The method also includes administering the compositions for wound healing following surgical or other invasive or traumatic procedures, for example to facilitate healing of skin or muscle damaged as the result of a surgical incision required during a surgical procedure, or to facilitate healing of a specific muscle, bone, or other tissue that was the subject of the surgical procedure, e.g., a bone, muscle, or a ligament or other tissue that was repaired by the surgical procedure.

The dosage methods and formulations of the invention used to treat tissue wounds can preferably include an amount of a folic acid compound that is greater than the DRI, e.g., in an amount greater than 400 mcg per day, preferably greater than 500 mcg per day,

e.g., greater than 1000 or 2000 mcg per day. Such an amount can be administered in a single oral dosage or two or more dosages taken at the same time or different times throughout the day. For example, a tablet of the invention may contain 1 mg of folic acid compound to be administered once a day.

In another embodiment, useful multivitamins for treating tissue wounds contain vitamin B_6, e.g., to provide a daily dosage in the range from about 5 to about 50 or 100 mg vitamin B_6 daily; and vitamin B_{12}, e.g., to provide a daily dosage in the range from about 20 to about 1000 mcg vitamin B_{12} daily. Useful multivitamins for treating tissue wounds can also include one or more additional vitamins and minerals such as vitamin C, e.g., to provide a daily dosage of an amount in the range from about 100 to about 500 mg vitamin C daily; vitamin E, e.g., to provide a daily dosage of an amount in the range from about 10 to about 50 IU Daily; thiamine, e.g., to provide a daily dosage of an amount in the range from about 5 to about 20 mg thiamine daily; riboflavin, e.g., to provide a daily dosage of an amount in the range from about 5 to about 20 mg riboflavin daily; niacin, e.g., to provide a daily dosage of an amount in the range from about 10 to about 50 mg niacin daily; as well as any other useful vitamins or minerals including biotin, panthothenic acid, copper, zinc, etc.

Pre-natal health and fetal development

Pre-natal health and fetal development can also relate to collagen, and can be promoted or improved by a diet that facilitates healthy collagen production. According to the invention, folic acid-containing compositions can be orally administered daily to promote collagen production in pregnant women to promote pre-natal health and development of fetal bone, muscle, and other tissue.

The dosage methods and formulations for pre-natal administration of folic acid-containing compositions according to the invention can preferably include an amount of a folic acid compound that is greater than the DRI, e.g., greater than 400 mcg per day, preferably greater than 500 or 600 mcg per day, e.g., greater than 1000 or 2000 mcg per day up to 5 mg or 10 mg per day of the folic acid compound. Such an amount can be administered in a single oral dosage or two or more dosages taken at the same time or different times throughout the day. For example, a tablet of the invention may contain

greater than 1 mg of folic acid compound, preferably 2 mg, or more, to be taken once daily.

In another embodiment, useful multivitamins for pre-natal administration can contain vitamin B_6, e.g., to provide a daily dosage of an amount in the range from about 5 to about 100 mg vitamin B_6 per day (which can be useful also in reducing nausea/vomiting during pregnancy); and vitamin B_{12}, e.g., to provide a daily dosage of an amount in the range from about 15 to about 100 mcg vitamin B_{12} per day, e.g., from about 40 to 75 mcg per day. Formulations according to the invention for pre-natal administration can also include one or more additional vitamins and minerals such as vitamin A, e.g., to provide a daily dosage of an amount in the range from about 2000 to about 5000 IU vitamin A per day; vitamin C, e.g., to provide a daily dosage of an amount in the range from about 125 to about 300 mg vitamin C; vitamin D, e.g., to provide a daily dosage of an amount in the range from about 200 to about 600 IU vitamin D per day; vitamin K, e.g., to provide a daily dosage of an amount in the range from about 20 mcg to about 200 mcg vitamin K per day; thiamine, e.g., to provide a daily dosage of an amount in the range from about 3.5 to about 5 or 10 mg thiamine per day; riboflavin, e.g., to provide a daily dosage of an amount in the range from about 3.5 to about 5 or 10 mg riboflavin per day; calcium, e.g., to provide a daily dosage in the range from about 200 to about 800 mg elemental calcium per day; magnesium, e.g., to provide a daily dosage of an amount in the range from about 25 to about 200 mg elemental magnesium per day; as well as any other useful vitamins or minerals.

Dermatological health and treatment or prevention of skin conditions

Collagen is also important to dermatological health, e.g., healthy skin. According to the invention, healthy skin can be promoted by facilitating healthy collagen production, and skin conditions may be treated or prevented by facilitating healthy collagen production. According to the invention, folic acid-containing compositions can be administered daily to promote collagen production and treat or prevent skin conditions or to promote healthy skin. Preferred administration routes are oral and topical administration.

The dosage methods and formulations of the invention used to promote healthy skin or treat or prevent skin conditions can preferably include an amount of a folic acid compound that is greater than the DRI, e.g., greater than 400 mcg per day, preferably greater than 500 mcg per day, e.g., greater than 1000 or 2000 mcg per day, up to 5 or 10 mg per day. Such an amount can be administered in a single oral dosage or two or more pills taken at the same time or different times throughout the day. For example, a tablet of the invention may contain 1 mg of folic acid compound and can be taken once daily.

In another embodiment, useful multivitamins for promoting healthy skin or treating or preventing skin conditions can contain vitamin B_6, e.g., to provide a daily dosage of an amount in the range from about 5 to about 100 mg vitamin B_6 per day; and vitamin B_{12}, e.g., to provide a daily dosage of an amount in the range from about 20 to about 1000 mcg or 1 mg vitamin B_{12} per day. Multivitamins according to the invention for promoting healthy skin or treating or preventing skin conditions can also include one or more additional vitamins and minerals such as vitamin A, e.g., to provide a daily dosage of an amount the range from about 2000 to about 4000 IU vitamin A per day; vitamin C, e.g., to provide a daily dosage of an amount in the range from about 125 to about 500 or 1000 mg vitamin C; as well as any other useful vitamins or minerals.

The described multivitamin formulations of this disclosure contain vitamins and minerals that do not require regulatory approval. The multivitamin formulations do not include aspirin or other pharmaceutical substances that in combination with the described vitamins and minerals would require regulatory approval for sale or use. The vitamins and minerals may be included in prescription or non-prescription amounts.

In one aspect, the formulations described herein can be prepared and used for treatment or prevention of diseases or conditions that relate to collagen, such as those described above. The formulations of the invention can include sufficient amounts of folic acid compound to facilitate healthy collagen production for treating or preventing the described conditions or for otherwise promoting healthy collagen for facilitating the production of healthy tissue that contains collagen. In some embodiments, the formulations preferably include therapeutic amounts of vitamin B_{12} and vitamin B_6. In other embodiments, the formulations can include additional vitamins and minerals that can treat or prevent a specific disease or condition or that can be administered for general

nutritional value. Aspirin or other substances that in combination with the described vitamins and minerals would require regulatory approval for sale or use, are not part of the multivitamin compositions of the invention.

Examples

Example OS for, e.g., osteoporosis

Example OS is a multivitamin tablet formulation that combines substances that can be administered to treat or prevent degenerative diseases or degenerative conditions such as degenerative bone disease, osteoporosis, Alzheimer's disease, and arthritis. The formulations include folic acid, vitamin B_6, and vitamin B_{12}, to promote healthy collagen production, and additionally include calcium and magnesium to diminish or prevent bone loss. The following dosage form can be taken or prescribed as two tablets taken once daily.

	DAILY DOSE	AMOUNT PER TABLET
FOLIC ACID	2.2 mg	1.1 mg
B_6	25 mg	12.5 mg
B_{12}	500 mcg	250 mcg
CALCIUM	600 mg	300mg
MAGNESIUM	300 mg	150 mg
VITAMIN D_3	15 mcg	7.5 mcg
BORON	3 mg	1.5 mg

Ingredients of certain commercially available formulations are shown in the table below. The formulations have less folic acid, vitamin B_6, vitamin B_{12}, calcium, magnesium, and boron, as compared to the Example OS formulation.

	EXAMPLE OS	CENTRUM® SILVER	TRI-BORON PLUS
FOLIC ACID	1.1 mg	400 mcg	--
B_6	12.5 mg	3 mg	--
B_{12}	250 mcg	25 mcg	--
CALCIUM	600 mg	200 mg	250 mg
MAGNESIUM	175 mg	100 mg	125 mg
VITAMIN D_3	7.5 mcg	10 mcg	2.5 mcg
BORON	1.5 mg	150 mcg	75 mcg

Recommended Nutrient Amount EXAMPLE OS:

NUTRIENT	AMOUNT PER TABLET	DAILY CONSUMPTION (ELEMENTAL AMOUNT)	RATIONALE
Calcium Carbonate	750 mg (300 mg elemental calcium)	600 mg elemental calcium (60% RDI)	Ca carbonate provides highest % elemental calcium; minimize tablet size
Magnesium Oxide	250 mg (150 mg elemental magnesium)	300 mg elemental magnesium (75% RDI)	Mg oxide provides highest % elemental Mg; minimize tablet size; below UL to minimize diarrhea
Folate	1.1 mg	2.2 mg	Promote healthy collagen
B_6	12.5 mg	25 mg	Promote healthy collagen
B_{12}	250 mcg	500 mcg	Promote healthy collagen
Boron	1.5 mg	3 mg	Amount from supplement plus common dietary intake well below UL
Vitamin D	7.5 mcg	15 mcg	Total daily dose equals DRI; well below UL

Example PN

EXAMPLE PN is a formulation that can be used to meet the nutritional needs of pregnant women in a convenient once daily vitamin satisfying all of the supplementation requirements for a pregnant woman. Prescribed as one tablet daily.

INGREDIENT	EXAMPLE PN	DRI PREGNANCY*
VITAMIN A (β-carotene)	2700 IU	2700 IU
VITAMIN C	150 mg	90 mg
VITAMIN D	400 IU	400 IU
VITAMIN E	30 IU	22 IU-33 IU
VITAMIN K	25 mcg	120 mcg
THIAMINE (B_1)	4 mg	1.2 mg
RIBOFLAVIN (B_2)	4 mg	1.3 mg
NIACIN	20 mg	16 mg
VITAMIN B_6	20 mg	1.7 mg
FOLIC ACID	2.0 mg	400 mcg
VITAMIN B_{12}	50 mcg	2.4 mcg
BIOTIN	30 mcg	30 mcg
PANTHOTHENIC ACID	10 mg	5 mg
CALCIUM	300 mg	1300 mg
IRON (carbonyl)	45 mg	18 mg
PHOSPHOROUS	100 mg	1250 mg
IODINE	150 mcg	150 mcg
MAGNESIUM	100 mg	400 mg
ZINC	15 mg	11 mg
SELENIUM	25 mcg	55 mcg
COPPER	0.5 mg	0.9 mg
MANGANESE	2.0 mg	2.3 mg
CHROMIUM	35 mcg	35 mcg
MOLYBDENUM	45 mcg	45 mcg
DOCUSTATE SODIUM	50 mg	

* DRI values for pregnancy have been included when available.

As compared to certain typical multivitamin formulations said to be useful for pre-natal nutritional supplementation, Example PN includes relatively higher daily dosages of folic acid, vitamin B_6, and vitamin B_{12}, vitamin C, thiamine, riboflavin calcium, and iron.

EXEMPLARY MULTIVITAMIN FORMULATIONS

INGREDIENT	EXAMPLE PN	PRENATE ADVANCED	PRECARE
VITAMIN A	2700 IU	5000 IU	None
VITAMIN C	150 mg	60 mg	120 mg
VITAMIN D	400 IU	400 IU	400 IU
VITAMIN E	30 IU	30 IU	30 IU
VITAMIN K	25 mcg	25 mcg	None
THIAMINE (B_1)	4 mg	1.5 mg	3 mg
RIBOFLAVIN (B_2)	4 mg	1.7 mg	3.4 mg
NIACIN	20 mg	20 mg	20 mg
VITAMIN B_6	20 mg	2 mg	3 mg
FOLIC ACID	2.0 mg	1000 mcg	1000 mcg
VITAMIN B_{12}	50 mcg	6 mcg	30 mcg
BIOTIN	30 mcg	30 mcg	15 mcg
PANTHOTHENIC ACID	10 mg	10 mg	10 mg
CALCIUM	300 mg	162 mg	40 mg
IRON	50 mg	18 mg	8 mg
PHOSPHOROUS	100 mg	109 mg	None
IODINE	150 mcg	150 mcg	150 mcg
MAGNESIUM	100 mg	100 mg	100 mg
ZINC	15 mg	15 mg	15 mg
SELENIUM	25 mcg	20 mcg	10 mcg
COPPER	0.5 mg	2 mg	2 mg
MANGANESE	2.0 mg	2 mg	None
CHROMIUM	35 mcg	120 mcg	15 mcg
MOLYBDENUM	45 mcg	75 mcg	15 mcg
DOCUSTATE SODIUM	50 mg	50 mg	None

EXAMPLE PS

EXAMPLE PS combines the benefits of vitamin B_{12}, vitamin B_6, and folic acid with additional vitamins and minerals for use in Pre/Post Surgery indications for treating and healing skin, muscle, or other tissue wounds, where healthy collagen production can facilitate such treatment or healing. The following exemplary formulation can be administered as one tablet daily.

INGREDIENT	AMOUNT PER TABLET	DRI
FOLIC ACID	1.0 mg	400 mcg
VITAMIN B_6	10 mg	1.7 mg
VITAMIN B_{12}	250 mcg	2.4 mcg
VITAMIN C	500 mg	90 mg
VITAMIN E	30 IU	22 IU-33 IU
THIAMINE (B_1)	10 mg	1.2 mg
RIBOFLAVIN (B_2)	5.0 mg	1.3 mg
NIACIN	20 mg	16 mg
BIOTIN	30 mcg	30 mcg
PANTHOTHENIC ACID	10 mg	5 mg
COPPER	1.0 mg	0.9 mg
ZINC	20 mg	40 mg

INGREDIENT	EXAMPLE PS	STRESS TABS	NEPHROVITE RX
FOLIC ACID	1.0 mg	400 mcg	1 mg
VITAMIN B_6	10 mg	5 mg	10 mg
VITAMIN B_{12}	250 mcg	12 mcg	6 mcg
VITAMIN C	500 mg	500 mg	60 mg
VITAMIN E	30 IU	30 IU	None
THIAMINE (B_1)	10 mg	10 mg	1.5 mg
RIBOFLAVIN (B_2)	5 mg	10 mg	1.7 mg
NIACIN	20 mg	100 mg	20 mg
BIOTIN	30 mcg	45 mg	300 mcg
PANTHOTHENIC ACID	10 mg	20 mg	10 mg
COPPER	1.0 mg	None	None
ZINC	11 mg	None	None

As compared to certain typical multivitamin formulations, Example PS includes a combination of relatively higher daily dosages of folic acid, vitamin B_6, and vitamin B_{12}, vitamin C, copper and zinc.

Example CP

EXAMPLE CP is a multivitamin formulation designed to combine the benefits of relatively high amounts of vitamin B_{12}, vitamin B_6, and folic acid with additional vitamins and minerals for use as a convenient high-potency multivitamin/multimineral. The following formulation can be taken as one tablet daily.

INGREDIENT	AMOUNT PER TABLET	DRI
VITAMIN A	3000 IU	3000 IU
VITAMIN C	500 mg	90 mg
VITAMIN D	400 IU	600 IU
VITAMIN E	30 IU	22 IU-33 IU

VITAMIN K	120 mcg	120 mcg
THIAMINE (B_1)	10 mg	1.2 mg
RIBOFLAVIN (B_2)	5.0 mg	1.3 mg
NIACIN	20 mg	16 mg
VITAMIN B_6	10 mg	1.7 mg
FOLIC ACID	1.0 mg	400 mcg
VITAMIN B_{12}	250 mcg	2.4 mcg
BIOTIN	30 mcg	30 mcg
PANTHOTHENIC ACID	10 mg	5 mg
CALCIUM	300 mg	1300 mg
IRON	18 mg	18 mg
PHOSPHOROUS	100 mg	1250 mg
IODINE	150 mcg	150 mcg
MAGNESIUM	100 mg	400 mg
ZINC	11 mg	11 mg
SELENIUM	25 mcg	55 mcg
COPPER	0.5 mg	0.9 mg
MANGANESE	2.0 mg	2.3 mg
CHROMIUM	35 mcg	35 mcg
MOLYBDENUM	45 mcg	45 mcg
LUTEIN	250 mcg	None established

INGREDIENT	EXAMPLE CP	CENTRUM	THERAGRAN M
VITAMIN A	3000 IU	5000 IU	5500 IU
VITAMIN C	500 mg	60 mg	120 mg
VITAMIN D	400 IU	400 IU	400 IU
VITAMIN E	30 IU	30 IU	30 IU
VITAMIN K	120 mcg	25 mcg	None
THIAMINE (B_1)	10 mg	1.5 mg	3 mg
RIBOFLAVIN (B_2)	5.0 mg	1.7 mg	3.4 mg
NIACIN	20 mg	20 mg	20 mg
VITAMIN B_6	10 mg	2 mg	3 mg
FOLIC ACID	1.0 mg	400 mcg	400 mcg
VITAMIN B_{12}	250 mcg	6 mcg	9 mcg
BIOTIN	30 mcg	30 mcg	15 mcg
PANTHOTHENIC ACID	10 mg	10 mg	10 mg
CALCIUM	300 mg	162 mg	40 mg
IRON	18 mg	18 mg	18 mg
PHOSPHOROUS	100 mg	109 mg	None
IODINE	150 mcg	150 mcg	150 mcg
MAGNESIUM	100 mg	100 mg	100 mg
ZINC	11 mg	15 mg	15 mg
SELENIUM	25 mcg	20 mcg	10 mcg
COPPER	0.5 mg	2 mg	2 mg
MANGANESE	2.0 mg	2 mg	None
CHROMIUM	35 mcg	120 mcg	15 mcg
MOLYBDENUM	45 mcg	75 mcg	15 mcg
LUTEIN	250 mcg	250 mcg	None
BORON	None	150 mcg	None
NICKEL	None	5 mcg	None
SILICON	None	2 mg	None
TIN	None	10 mcg	None
VANADIUM	None	10 mcg	None

As compared to certain typical multivitamin formulations, Example CP includes relatively higher daily dosages of folic acid, vitamin B_6, vitamin B_{12}, vitamin C, vitamin K, thiamine, riboflavin, and calcium.

Example D

EXAMPLE D contains a combination of essential vitamins/minerals for promoting healthy skin, e.g., for facilitating and maintaining healthy skin, or for treating or preventing a specific skin condition such as acne, rashes, etc. The following formulation can be taken as one tablet daily.

INGREDIENT	AMOUNT PER TABLET	DRI
FOLIC ACID	1.0 mg	400 mcg
VITAMIN-A (βcarotene)	3000 IU	3000 IU
VITAMIN B_6	10 mg	1.7 mg
VITAMIN B_{12}	250 mcg	2.4 mcg
VITAMIN C	500 mg	90 mg
VITAMIN E	200 IU	22 IU-33 IU
RIBOFLAVIN (B_2)	5.0 mg	1.3 mg
Niacin	20 mg	16 mg
Biotin	30 mcg	30 mcg
Selenium	25 mcg	55 mcg
Zinc (sulfate)	30 mg	15 mg

INGREDIENT	EXAMPLE D	DERMAVITE
FOLIC ACID	1.0 mg	400 mcg
VITAMIN-A (βcarotene)	3000 IU	3,500 IU
VITAMIN B_6	10 mg	10 mg
VITAMIN B_{12}	250 mcg	None
VITAMIN C	500 mg	120 mg
VITAMIN E	200 IU	60 IU
RIBOFLAVIN (B_2)	5.0 mg	8.5 mg
NIACIN	20 mg	None
BIOTIN	250 mcg	600 mcg
SELENIUM	25 mcg	50 mcg
ZINC (SULFATE)	30 mg	45 mg
COPPER	None	2 mg
MANGANESE	None	5 mg
CHROMIUM	None	200 mcg
CALCIUM	None	270 mg
SILICON	None	20 mg
LYCOPENE	None	5 mg

EXAMPLE D INGREDIENT RATIONALE

INGREDIENT	BENEFITS
FOLIC ACID	Healthy cell division and for protein and DNA synthesis.
VITAMIN A	Helps maintain the health of the skin and regulates skin cell growth.
VITAMIN B_6	Important enzyme cofactor.
VITAMIN B_{12}	Maturation of RBCs and DNA synthesis.
VITAMIN C	Essential for collagen production. Aids in tissue repair and cell regeneration.
VITAMIN E	Protects cells from oxidative damage and wrinkling.
VITAMIN B_2	Deficiency may produce a defect in collagen synthesis.
NIACIN	Deficiency may produce dermatitis like symptoms.
BIOTIN	Necessary for metabolism and growth. Required by healthy nails and skin.
SELENIUM	Antioxidant that preserves tissue elasticity.
ZINC	Important in tissue and cell growth.